1. Current literature highlights

1.1 Thrombin inhibitors

Thrombin is a trypsin-like serine protease which plays a crucial role in blood coagulation by cleaving soluble fibrinogen into fibrin. Subsequent polymerisation of fibrin stabilises the initially formed thrombozyte clots at the site of blood vessel damage. Undesired activation of the blood coagulation cascade can result in cardiovascular disorders such as deep vein thrombosis, myocardial infarction, unstable angina, pulmonary embolism and ischaemic stroke. Thrombin has therefore become an important target for the treatment of thromboembolic diseases.

Approaches to thrombin inhibitors have centred around the D-Phe-Pro-Arg motif that mimics the natural substrate. D-Phe replaces the Phe residue in fibrinogen which normally occupies the lipophilic D pocket. The guanidine moiety of Arg which is also present in the natural substrate forms a salt bridge with Asp189 at the bottom of the specificity pocket of thrombin. Interactions with Ser195 in the active centre of thrombin were shown not to be essential for high affinity to the enzyme. In an effort to optimise potency and selectivity of thrombin inhibitors, a combinatorial chemistry approach was undertaken [1].

A small library was synthesised on 4-nitrophenyl carbonate Wang-resin (Novabiochem) in an attempt to generate potent thrombin inhibitors. The library compounds were evaluated in a chromogenic assay and one of the most potent compounds found was (i) which possesses a thrombin inhibition IC_{50} of 3.6 nM.

1.2 Liver X receptor agonists

The increased incidence of cardiovascular disease (CVD) in westernised nations has been linked to increased dietary intake of cholesterol and saturated fats and an increase in low-density lipoprotein (LDL) particles. Accumulation of small, dense LDL particles in the arterial wall leads to the formation of cholesterol laden foam cells, which are the hallmark of coronary atherosclerosis, and activation of the immune system. Although cholesterol-lowering drugs such as statins reduce the incidence of CVD in patients with high circulating levels of LDL cholesterol (LDLc), atherosclerosis also afflicts individuals with relatively normal levels of LDLc. In contrast to LDL, the levels of high-density lipoprotein (HDL) particles are inversely related to the incidence of CVD. The protective role of HDL may result from its role in mediating ‘reverse cholesterol transport’ whereby cholesterol is transported from peripheral cells back to the liver. Thus agents that promote reverse cholesterol transport by raising circulating levels of HDL could provide an alternative therapeutic option for the prevention of atherosclerotic CVD.

The liver X receptors, LXRa (NR1H3) and LXRb (NR1H2) are oxysterol-activated transcription factors that belong to the nuclear hormone receptor superfamily. It has been proposed that compound (ii) is an endogenous ligand for LXRa in the liver. Upon cholesterol feeding, the hepatic levels of (ii) are raised.
in rats to levels consistent with its putative role as a natural LXRα agonist.

The identification of a novel chemical series of LXR agonists through solid-phase parallel synthesis of tertiary amines has recently been reported [2]. A library of 1280 compounds was synthesised on Rink amide solid phase resin, the design of which was based on the GlaxoSmithKline high-throughput screening hit (iii).

The library compounds were screened for activity in the cell-free ligand-sensing assay (LiSA) for human LXRα. The LXRα LiSA measures the ligand-dependent recruitment of a 24 amino acid fragment of the steroid receptor coactivator 1 (SRC1) to the ligand-binding domain of the receptor. One of the most potent compounds isolated was (iv) which possessed an EC50 of 45 nM in the LXRα/SRC1 LiSA. This work has provided a novel, potent lead for the development of drugs to increase reverse cholesterol transport and further work in this area is warranted.

2. A summary of the papers in this month’s issue.

2.1 Solid-phase synthesis

Solid-phase cross metathesis of supported styrenyl ether with styrene derivatives has produced stilbenoids in high yields [3]. A novel synthesis of 2,3,5-trisubstituted 4H-imidazolones on Merrifield resin has been reported [4]. A new approach for the synthesis of phosphine-oxazoline peptide ligands by solid-phase methods has been published [5]. 2,6,9-Trisubstituted purines have been synthesised from resin-bound 6-thiopurines using a traceless solid-phase method [6]. Free radical addition of haloalkanes to polymer-bound olefins has been used in the solid-phase synthesis of pyrethroids [7]. Merrifield-supported o-cresol undergoes electrophilic aromatic chlorination using SO2Cl2 resulting in para/ortho ratios in excess of 50 [8]. A versatile method for the solid-phase synthesis of 3,5-disubstituted oxazolidin-2-ones has been described [9]. The solid-phase synthesis of 2-substituted-3-(substituted sulphanyl)-1,2,4-benzothiadiazine 1,1-dioxide has been developed [10]. 4,6-Dichloro-2-(methylthio)-5-nitropyrimidine has been used as a building block for an efficient nine-step synthesis of olomoucine. [11].

The solid-supported synthesis of functionalised 1,2,4-triazin-6-ones from resin-bound amino acids and acid chlorides has been described [12].

2.2 Solution-phase synthesis

Diverse 4-thiazolidinones have been assembled by DCC-mediated three-component reactions of amines, aldehydes and mercaptoacetic acid [13]. A method for the solution-phase synthesis of substituted imidazoles from cyclic or acyclic 1,2-aminoalcohols has been used to prepare libraries of fused imidazole-azepines [14]. Soluble-polymer-supported synthesis of Biginelli compounds has been used to prepare 3,4-dihydropyrimidin-2(1H)-ones [15]. A method for the solid-phase synthesis of a-sulphonylamino amides has been developed using an Ugi-type 4-component condensation [16].

2.3 Library intermediates

Twenty-four bifunctional diketopiperazines with the potential for incorporation into combinatorial libraries have been synthesised [17].

2.4 Solid-supported reagents

Isonitriles have been successfully synthesised by the use
of microwave irradiation and solid-supported sulphonyl chlorides [18].
Cis-constrained norstatine analogues have been prepared using a trimethylsilyl azide-modified Passerini three-component reaction [19].
A novel method for the synthesis of protected guanidines relies on the use of polystyrene-supported carbodiimide [20].
Manganese porphyrin catalysts have been supported on Merrifield and Argogel resins and used for alkene epoxidation [21].
A chiral polymer-supported sulphonamide has been used to catalyse the enantioselective reduction of β-keto sulphones [22].

2.5 Novel resins, linkers and techniques
A new multidetachable linker has been used to prepare libraries of sulphamates and phenols [23].
Cyclopentadienylmanganese tricarbonyl resins have been used as potential olefin traceless supports [24].
Chiral enzyme inhibitors have been immobilized on solid supports by amid-forming coupling and olefin metathesis and used to for lipase inhibition studies [25].

2.6 Library applications
The use of the triterpenoid lupeol as a scaffold for the solid-phase synthesis of libraries, tested for in vitro antimalarial activity, has been described [26].
A combinatorial library of indinavir analogues has been synthesised on solid support in order to find a replacement for the aminoidanol moiety [27].
Benzofurans have been prepared on solid support and investigated as selective estrogen receptor modulators [28].
Two structural classes of dual α4β1/α4β7 integrin antagonists have been investigated using solid-phase parallel synthesis [29].
Parallel synthesis has been used to explore the SAR of acyl dipeptide reversible caspase inhibitors [30]. A new structural class has been optimised for activity against caspasases 1,3,6,7, and 8 [31].
A general solid-phase method has been developed to prepare novel cyclic ketone inhibitors of the cysteine protease cruzain [32].
The incorporation of acidic functionality into a combinatorial library-derived CCR5 antagonist has resulted in compounds with enhanced anti-HIV-1 activity [33].
Parallel solution and solid-phase methods have been used to synthesise spiropyrazolone derivatives as neurokinin-1 receptor ligands [34].
Parallel synthesis of 31 sulphamides has led to the discovery of a potent antimalarial compound [35].
Screening of a solid-phase peptide library has delivered a dsDNA binding molecule with preference for pyrimidine sequences [36].
A purine-scaffold based library has been employed in the discovery of a novel class of HSP90 molecular chaperone inhibitor [37].
The synthesis of a P1 arginine peptide combinatorial library has been used to determine substrate specificity of serine peptidases [38].
A focused library of di- and tri-peptidomimetics have been designed and synthesised as possible ACE inhibitors [39].
A structurally diverse carbohybrid library has been used to identify novel inhibitors of fibroblast growth factor (FGF-2) binding to heparin [40].
An efficient method for the solid-phase synthesis of tripeptide-bearing glycopeptide antibiotics has been used to generate a combinatorial library of derivatives of chloroorienticin B [41].
Parallel solution- and solid-phase synthesis of spiropyrrleo-pyrrole libraries has been used in the search for novel neurokinin receptor ligands [42].

References
Further reading list

Papers on combinatorial chemistry or solid-phase synthesis from other journals


A solid-supported, enantioselective synthesis suitable for the rapid preparation of large numbers of diverse structural analogues of (-)-saframycin A. Myers, A.G.; Lanman, B.A. Journal of the American Chemical Society (2002), 124(44), 12969-12971.

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